REMARKS/ARGUMENTS

Status of the Claims

Claims 1-11 are pending. Claims 1-4 and 6-11 would be amended. Claims 29-36 are newly presented for examination. Claim 7 is canceled. After entry of these amendments, claims 1-6, 8-11 and 29-36 would be pending. The amendments and claim cancellations are made without prejudice.

Claims 3, 8, and 11 currently stand objected to for an alleged lack of clarity.

Claims 3 and 6-11 currently stand rejected under 35 U.S.C. §112 as allegedly being indefinite.

Claims 3, 8, 10 and 11 currently stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

Claims 6 -9 currently stand rejected under 35 U.S.C. §112, second paragraph as allegedly failing to recite an essential step.

Claims 10 and 11 currently stand rejected under 35 U.S.C. §112, second paragraph as allegedly lacking a proper antecedent basis.

Claims 1-9 currently stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description.

Claims 1-9 currently stand rejected under 35 U.S.C. §112, first paragraph for an alleged want of written description.

Applicants respectfully respond to the above rejections below.

Support for the Amendments to the Claims

Claim1 would be amended to recite:

> A method of screening for a splicing defect in a human dihydropyrimidine dehydrogenase gene wherein said gene comprises the sequence of SEQ ID NO:1 or the variant thereof wherein the residue at position 434 is an A and wherein said defect causes the exon of SEQ ID NO:1 to be skipped, said method comprising determining whether said gene has an A residue or a G residue at said position 434, wherein said

method the presence of an A residue, but not a G residue, at said position 434 indicates the presence of the splicing defect causing the exon of SEQ ID NO:1 to be skipped.

Support for the above subject matter is found in the specification *inter alia* in Figures 1A, 1B and 3, at p. 3, first paragraph of the Summary, at p. 4, 3rd full paragraph, and at p.8, 2nd paragraph.

Claim 2 would be amended to recite:

"The method of claim 1, wherein the method comprises the step of amplifying a fragment of said gene comprising position 434 of SEQ ID NO:1 and detecting a G residue or an A residue at said position of said fragment."

Support for this subject matter is found in the previous version of the claim and in the specification at p. 11.

Claim 3 would be amended to recite:

"The method of claim 2, wherein the method comprises amplifying the fragment with a polymerase chain reaction primer from about 15 to about 20 nucleotides long and wherein said primer the nucleotides are in a sequence exactly complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861."

Support for the subject matter of "15 to 20 nucleotides long" is found *inter alia* at p. 15, line 24. Support for the subject matter of exactly complementary is found *inter alia* in the specification at p. 15, lines 10-13 and also at p. 18, first 3 lines, the paragraph bridging pages 18 and 19, and in the Examples which used DELR1 and DELF1 (see paragraph bridging pp. 21 and 22).

Claim 4 would be amended to recite:

"The method of claim 2 wherein the detecting is by digestion of the amplified fragment with a Mae II restriction endonuclease."

Support for the recital of "fragment" is found *inter alia* in the antecedent of the base claim.

Claim 6 would be amended to recite:

A method of screening a human for sensitivity to 5-fluorouracil, comprising:

(a) isolating genomic DNA from the human, said genomic DNA comprising the sequence of SEQ ID NO:1 or comprising the

variant of the sequence of SEQ ID NO:1 wherein the residue at position 434 is an A;

(b) amplifying under stringent conditions a fragment of the genomic DNA comprising position 434 of SEQ ID NO:1; and

(c) determining whether the amplified fragment has an A or G residue at position 434; wherein the substitution of an A residue by a G residue at position 434 indicates the patient is sensitive to 5-fluorouracil.

Support for this subject matter is generally as set forth above for claim 1. The subject matter particularly related to 5-fluorouracil is supported *inter alia* in original claim 6. Support for the "isolating" subject matter is found in the specification *inter alia* in the section of the same title at p. 8. Support for the "amplifying" subject matter is found in the specification at p. 11, original claim 3, and in the paragraph bridging pages 7 and 8.

Claim 8 would be amended to depend from claim 6 rather than canceled claim 7. The claim was also amended to recite:

"The method of claim 6 wherein said primer the nucleotides are in a sequence exactly complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861."

Support for this recital is as set forth above for claim 3.

Claim 9 would be amended to change its dependency from canceled claim 7 to claim 6. Support for the subject matter is found *inter alia* in the recitals of previous claims 6, 7, and 8.

Claim 10 would be amended to recite:

"A composition comprising a polymerase chain reaction primer from about 15 to 20 nucleotides long wherein said primer the nucleotide sequence is exactly complementary to a nucleotide sequence of SEQ ID NO: 1 located between position 434 and position 861."

Support for this subject matter is as set forth above for claim 3.

Claim 11 would be amended to more clearly set forth the antecedent by reciting "said primer." Support for this amendment is found *inter alia* in the previous version of the claim.

New claim 29 would recite:

> A method of testing a human for a single nucleotide polymorphism at position 434 of SEQ ID NO:1, the method comprising:
>
> a) isolating a sample from the human of genomic DNA wherein the genomic DNA comprises the nucleotide sequence of SEQ ID NO:1 or comprises the variant thereof wherein the nucleotide corresponding to position 434 of SEQ ID NO:1 is A;
>
> b) selectively amplifying a fragment of the genomic DNA wherein the amplified fragment comprises position 434 of SEQ ID NO:1; and
>
> c) determining whether the residue at position 434 of SEQ ID NO:1 is an A or a G.

Support for the subject matter of polymorphism is found *inter alia* at p. 15, 2nd paragraph, Figs. 1A, 1B, and 3, and SEQ ID NO:1. Support for the remainder of the claim is as set forth above claim 1.

New claim 30 would depend from claim 29 and recite:

> "The method of claim 29, wherein the fragment of genomic DNA is amplified with a polymerase chain reaction primer from about 15 to about 20 nucleotides long and wherein said primer the nucleotides are in a sequence exactly complementary to a sequence of SEQ ID NO: 1 located between position 434 and 861."

Support for this recital is as set forth above for claim 3.

New claim 31 would depend from claim 29 and recite:

> "The method of claim 29, wherein the determining is by digestion of the amplified fragment with a Mae II restriction endonuclease."

Support for this subject matter is found *inter alia* in original claim 4.

New claim 32 would depend from claim 29 and recite:

"The method of claim 29, wherein the determining is by oligonucleotide array."

Support for this subject matter is found *inter alia* in original claim 5.

New claim 33would recite:

"A composition comprising a polymerase chain reaction primer from about 15 to about 20 nucleotides long wherein said primer the nucleotide sequence is exactly complementary to a nucleotide sequence of SEQ ID NO: 1 located between position 1 and position 268."

Support for this subject matter is found *inter alia* in original claims 2 and 11, SEQ. ID NO:1, and in the paragraph at p. 15, last two paragraphs.

New claim 34 would recite:

"A composition of claim 33, wherein the sequence of the primer is the sequence of SEQ ID NO:3."

Support for this subject matter is set forth *inter alia* in SEQ ID NO:3.

New claim 35 would recite:

"A composition of claim 10, wherein the sequence of the primer is the sequence of SEQ ID NO:4."

Support for this subject matter is set forth *inter alia* in SEQ ID NO:4.

New claim 36, would depend from claim 29 and recite:

"The method of claim 29, wherein the residue at position 434 of SEQ ID NO:1 is an A."

Support for this subject matter is as set forth for claim 29.

In view of the above, Applicants submit that the amendments to the claims add no new matter and respectfully request their entry.

Response to the Rejection of Claims 3, 8, and 11 for an Alleged Lack of Clarity

Claims 3, 8, and 11 have been amended as suggested by the Examiner to clarify the antecedent basis of the recital "nucleotides."

In view of the above, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 3, 8, 10, and 11 for Alleged Indefiniteness.

The Action alleged that the recital of "complementary" was indefinite as it was alleged to be unclear as to whether the probes were completely or partially complementary to the fragments of the polynucleotide of SEQ ID NO.1. Without acquiescing to the position of the Examiner and in order to expedite prosecution, the Applicants have amended claims 3, 8, and 10 to recite the term "exactly complementary." As claim 11, depends from claim 10, the amendment to claim 10 is understood to render moot the objection to claim 11.

In view of the above, Applicants respectfully request that the above amendments be reconsidered and withdrawn.

Response to the Rejection of Claims 6-9 for an Alleged Missing Step.

Without acquiescing to the position of the Examiner and in order to expedite prosecution of the application, Applicants have amended the base claim to recite the allegedly missing subject matter.

In view of the above, Applicants request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claim 10 for an Alleged Indefiniteness.

Applicants thank the Examiner for pointing out the need to explicitly set forth the antecedent basis for the recital and have so amended the claim.

In view of the above, Applicants request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 1-9 for an Alleged Lack of Written Description.

The Examiner rejected the above claims on the grounds that the specification did not provide adequate written description of the dihydropyrimidine dehydrogenase genomic DNA. Without acceding to the Examiner's position and in order to expedite prosecution of the application, Applicants have amended base claim 1 to recite:

> A method of screening for a splicing defect in a human dihydropyrimidine dehydrogenase gene wherein said gene comprises the sequence of SEQ ID NO:1 or the variant thereof wherein the residue at position 434 is an A and wherein said defect causes the exon of SEQ ID NO:1 to be skipped, said method comprising determining whether said gene has an A residue or a G residue at said position 434, wherein said method the presence of an A residue, but not a G residue, at said position 434 indicates the presence of the splicing defect causing the exon of SEQ ID NO:1 to be skipped.

In addition, claim 6 has also been amended to recite in part:

> genomic DNA comprising the sequence of SEQ ID NO:1 or comprising the variant of the sequence of SEQ ID NO:1 wherein the residue at position 434 is an A;

As noted previously, base claims 1 and 6 are not composition claims. Instead, these claims are drawn to methods whose essential genomic or DPD DNA subject matter lies within the bounds of SEQ ID NO:1. Claim 1, as amended, is drawn to a method of detecting a DPD gene "having a splicing defect which causes the exon of SEQ ID NO:1 to be skipped." This claim further sets forth methods operating upon genomic or DPD DNA having the sequence of SEQ ID NO:1 in which the residue at position 434 is either a G or an A. The recitals pertaining to SEQ ID NO:1 encompass all the genomic DNA or DPD gene subject matter essential to practicing the invention. These recitals encompass the sequence of the skipped exon, the exon's flanking intronic sequences, and the splice site G to A polymorphs. This subject matter is amply described throughout the specification.

Most importantly, the genomic subject matter outside the bounds of SEQ ID NO:1 is *not* essential subject matter. Assuming for the sake of argument, a relevant number of polymorphisms of the DPD genome (such as the one identified in the WO/ 95/28489 reference

identified by the Examiner) could occasionally be found outside the bounds of SEQ ID NO:1, claim 1 is drawn to a method of detecting those DPD polymorphs having a particular splicing defect which causes skipping of the exon of SEQ ID NO:1. For any such polymorphs, skipping of this exon would be expected to delete about a 55 amino acid fragment of the DPD protein. Such a large deletion, regardless of any potential additional polymorphic form outside the bounds of SEQ ID NO:1, would be strongly expected by one of ordinary skill in the art to produce a protein deficient in DPD activity. The references cited by the Examiner support this proposition. They were cited to show how a few amino acid substitutions can alter or destroy the activity of a protein. The loss of the about 55 amino acids of the subject skipped exon can similarly be reasonably expected to have a drastic effect regardless of a polymorphic form outside SEQ ID NO:1. Not surprisingly, clinicians as noted in Vreken et al. *J. Inher. Metabl. Dis.* 19:645-654 (1996)(already of record) would recognize the predictive value of such a screening method. Considering the above, Applicants respectfully submit that one of ordinary skill in the art would know that the Applicants were in possession of the subject matter of claims 1-9 at the time the application was filed.

Claims 6 and 29 are similarly drawn to methods operating on genomic subject matter of SEQ ID NO:1 wherein the residue at position 434 can be an A or a G and the above arguments should apply with equal force to their substance. Thus, in view of the above, Applicants submit that the claims as amended are drawn to a disclosed structural feature (the exon skipping mutation of SEQ ID NO:1) which effectively constitutes the most important structural feature of any such DPD polymorph genus and that the relationship between the structural feature and its activity (i.e., skipping the exon causes a deletion of a large portion of the DPD protein) is fully set forth in the specification.

As one of skill in the art would recognize that the applicant was in possession of the necessary or essential common attributes or features of the elements possessed by the recited genus, Applicants respectfully request reconsideration and withdrawal of the above rejections.

Response to the Rejection of Claims 1-9 for an Alleged Want of Enablement

Without acquiescing to the position of the Examiner and in order to facilitate prosecution of the application, Applicants have amended the base claims to more particularly set forth the subject matter of the genomic or DPD DNA having the sequence of SEQ ID NO:1 wherein the residue at position 434 can be an A or G. Applicants believe the amendment fully addresses the concerns identified by the Examiner.

Applicants further note that the claims relate to detecting a polymorphism at position 434 which is associated with a skipping of the exon of SEQ ID NO:1, deletion of about 55 amino acids from the encoded DPD protein, and deficiency in DPD protein activity. Claim 1 is drawn to a method of detecting a particular splicing defect leading to skipping of the exon of SEQ ID NO:1, claim 6 is drawn to a method of screening a human for sensitivity to 5-fluorouracil, and claim 29 is drawn to a method of detecting the polymorphism.

In view of the above, Applicants respectfully request that the above rejections be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

Frank J. Mycroft
Reg. No. 46,946

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
FJM:fjm
60100911 v1